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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/529,722	Applicant(s) SQUIRRELL ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) 18 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☒ Claim(s) 14 is/are objected to.

8)☒ Claims 1-18 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-17, drawn to a recombinant cell, method for producing a recombinant cell and a method for producing a polypeptide product using a recombinant cell.

Group II, claim 18, drawn to a polypeptide product which is substantially free of an undesired protein.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The groups comprise products that are unrelated, i.e., the product of Group I is a recombinant cell, while the product of Group II is a polypeptide product. Furthermore, the polypeptide product of Group II does not constitute a special technical feature as defined by PCT Rule 13.2, as polypeptide products that are substantially free of undesired proteins are known in the prior art, for example, "Firefly luciferase purification using

polyethylene glycol and Dyemetrex Orange A", *J. Chromatogr.* (1995), 695:33-40 describes a method for producing luciferase that is substantially free of adenylate kinase.

During a telephone conversation with Arthur R. Crawford on 10/24/00 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-17. Affirmation of this election must be made by applicant in replying to this Office action. Claim 18 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Production of Luciferase that is Free of Adenylate Kinase Activity"

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required. See MPEP § 608.01(b).

4. Claim 14 is objected to because of the following informalities: The claim does not terminate with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 6, 10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "activity" in claim 1 is a relative term which renders the claim indefinite. The term "activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the language "activity" be replaced with "enzymatically active".

The term "stable" in claims 1, 10, 15 and 16 is a relative term which renders the claim indefinite. The term "stable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. It is suggested that the language "stable" be replaced with, for example, "at least 50 % enzymatic activity".

The term "unstable" in claims 1, 2, 10, 15, and 16 is a relative term which renders the claim indefinite. The term "unstable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the language "unstable" be replaced with, for example, "less than 50 % enzymatic activity".

The term "intact" in claims 3 and 6 is a relative term which renders the claim indefinite. The term "intact" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the language "intact" be replaced with, for example, "at least 50 % enzymatic activity".

The term "elevated temperatures" in claim 4 is a relative term which renders the claim indefinite. The term "elevated temperatures" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. ***.

Claims 5, 7-9, 11-14, and 17 are rejected as being dependent on indefinite claims 1-4, 6, 10, 15 and 16.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6, 10, and 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing and recovering luciferase that is substantially free of a mutant *Escherichia coli* adenylate kinase that is enzymatically inactive at temperatures greater than or equal to 37 °C using recombinant cells therefore, and methods of producing said cells, does not reasonably provide enablement for a method for producing any polypeptide product that is substantially free of any mutated undesired protein that is unstable under any conditions at which the polypeptide product remains stable using recombinant cells therefore and methods of producing said cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3 (claims 4, 5, and 7-9 dependent thereon), 6 , 10 (claims 11-14 dependent thereon), 15 (claim 17 dependent thereon) and 16 are so broad as to encompass a method of producing any polypeptide or protein as either a polypeptide product, desired product or recovered product free of an undesired protein, wherein the conditions at which the undesired protein is denatured or unstable and the polypeptide product, desired product or recovered product is stable or intact are any conditions using recombinant cells therefore and methods of producing said cells. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptide products or undesired proteins. In the instant case, the disclosure is limited to a method for production and recovery of luciferase that is substantially free of a mutant *Escherichia coli* adenylate kinase that is

enzymatically inactive at temperatures greater than or equal to 37 °C using recombinant cells therefore, and methods of producing said cells.

The specification does not support the broad scope of the claims which encompass a method of producing any polypeptide product that is substantially free of any undesired protein under any conditions that would denature an undesired protein while the polypeptide product remains intact using recombinant cells therefore, and methods of producing said cells, because the specification does not establish: a) the methods for isolating and mutating any undesired protein such that the undesired protein becomes unstable under some condition at which the desired remains stable; b) the conditions that denature any undesired protein while any polypeptide product remains intact c) the general tolerance of the method to modification and extent of such tolerance; d) a rational and predictable scheme for modifying any steps in the methods involved with an expectation of obtaining a functional polypeptide product free of the undesired protein; and e) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polypeptide products or undesired proteins. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5 and 7-17 rejected under 35 U.S.C. 103(a) as being unpatentable over Backman et al. (EP 373 962) in view of Kajiyama et al. (US Patent 5,229,285), Liang et al. (Gene 80:21-28), Kiel et al. (Mol Gen Genet 207:294-301) and Belinga et al. (J Chromatogr A 695:33-40). Claims 1-5 and 7-17 are drawn to a method for producing and recovering luciferase that is substantially free of a thermolabile *Escherichia coli* adenylate kinase using recombinant cells therefore, and methods of producing said cells.

Backman et al. teach a method of isolating a thermostable enzyme free of undesired contaminants. The method includes heating the enzyme and the unwanted contaminants to a temperature sufficient to inactivate the unwanted contaminants but not sufficient to inactivate the thermostable enzyme.

Kajiyama et al. teach a method for preparing a vector that encodes a thermostable firefly luciferase and the expression of thermostable firefly luciferase using said vector in a host cell. The thermostability of firefly luciferase retains 80 % or greater activity following a 20 minute incubation at 50 °C and 65 % or greater activity following a 60 minute incubation at 50 °C.

Liang et al. teach the isolation and cloning of a chromosomal gene for a thermolabile *Escherichia coli* adenylate kinase. The thermolabile *Escherichia coli* adenylate kinase has a leucine to glutamine amino acid substitution at position 107 that results in heat inactivation of the thermolabile *Escherichia coli* adenylate kinase at 40 °C.

Kiel et al. teach a method for introducing a mutated gene into the *Escherichia coli* chromosome by homologous recombination between the chromosome and a plasmid carrying the mutant gene. Furthermore, Kiel et al. suggest that this method should be applicable to construction of mutants for any *Escherichia coli* chromosomal gene.

Belinga et al. teach the advantages of purifying luciferase from adenylate kinase for the purpose of a bioluminescent assay. In particular, removing adenlyate kinase from luciferase reduces background bioluminescence relative to a non-purified luciferase preparation.

Backman et al. teach a method of isolating a thermostable enzyme free of undesired contaminants, said method including heating the enzyme and the unwanted contaminants to a temperature sufficient to inactivate the unwanted contaminants but not sufficient to inactivate the

thermostable enzyme. Kajiyama et al., Liang et al., Kiel et al. and Belinga et al. teach a method of preparing a thermostable luciferase, a method of preparing a plasmid vector with a gene encoding a thermolabile *Escherichia coli* adenylate kinase, a method of replacing *Escherichia coli* chromosomal genes with a mutant gene using a plasmid vector and the advantages of purifying luciferase from adenylate kinase for use in bioluminscent assays. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Backman et al., Kajiyama et al., Liang and Glaser, Kiel et al. and Belinga et al. for a method of producing and recovering luciferase that is substantially free of a thermolabile *Escherichia coli* adenylate kinase using recombinant cells therefore, and methods of producing said cells. One would be motivated to replace the wild-type adenylate kinase gene with the thermolabile adenylate kinase gene of Liang et al. such that one could easily produce and recover luciferase that is substantially free of thermolabile *Escherichia coli* adenylate kinase by the methods taught by Backman et al., (i.e., heat denaturation of the thermolabile contaminant). One would have a reasonable expectation of success for producing and recovering luciferase that is substantially free of a thermolabile *Escherichia coli* adenylate kinase using recombinant cells therefore, and methods of producing said cells because of the results of Backman et al., Kajiyama et al., Liang et al., Kiel et al. and Belinga et al. Therefore, claims drawn to a method for producing and recovering luciferase that is substantially free of a thermolabile *Escherichia coli* adenylate kinase using recombinant cells therefore, and methods of producing said cells would be obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934.

The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

November 06, 2000